(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 702 555 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
11.03.1998 Bulletin 1998/11

(21) Application number: **94916236.6**

(22) Date of filing: **13.05.1994**

(51) Int. Cl.[6]: **A61K 31/505**

(86) International application number:
PCT/EP94/01580

(87) International publication number:
WO 94/28902 (22.12.1994 Gazette 1994/28)

(54) PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

PYRAZOLPYRIMIDINONE FÜR DIE BEHANDLUNG VON IMPOTENZ

PYRAZOLOPYRIMIDINONES UTILISEES POUR TRAITER L'IMPUISSANCE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **09.06.1993 GB 9311920**

(43) Date of publication of application:
27.03.1996 Bulletin 1996/13

(73) Proprietors:
- **Pfizer Limited**
  Sandwich Kent CT13 9NJ (GB)
  Designated Contracting States:
  GB
- **Pfizer Research and Development Company, N.V./S.A.**
  Dublin 1 (IE)
  Designated Contracting States:
  BE CH DE DK ES FR GR IE IT LI LU NL PT SE AT

(72) Inventors:
- **ELLIS, Peter**
  Ramsgate Road Sandwich Kent CT13 9NJ (GB)
- **TERRETT, Nicholas Kenneth**
  Sandwich Kent CT13 9NJ (GB)

(74) Representative:
Moore, James William, Dr. et al
Pfizer Limited
Ramsgate Road
Sandwich Kent CT13 9NJ (GB)

(56) References cited:
EP-A- 0 463 756 **EP-A- 0 526 004**

- **BR. J. PHARMAC. vol. 81, no. 4 , 1984 pages 665 - 674 A. BOWMANN ET AL. 'Cyclic GMP mediates neurogenic relaxation in the bovine retractor penis muscle'**
- **AM. J. PHYSIOL. vol. 264 , February 1993 pages H419 - H422 F. TRIGO-ROCHA ET AL. 'Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs'**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 702 555 B1

Description

This invention relates to the use of a series of pyrazolo[4,3-d]pyrimidin-7-ones for the preparation of a medicament for the treatment of impotence.

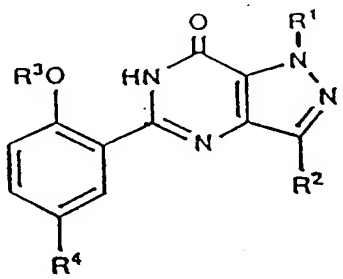
Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):



(I)

wherein

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;

R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;

R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached

form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}$N)C_2-C_6 alkyl; ($R^{13}R^{14}$NOC)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or C(NH)$NR^{13}R^{14}$;

and

R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms, alkenyl and alkynyl groups having four or more carbon atoms, alkoxy groups having three carbon atoms and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore, certain compounds of formula (I) which contain alkenyl groups may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; CH=CHCONR^{5}R^6; CH=CHCO$_2$R^7; CONR^{5}R^6; CO$_2$H; Br; NR^{5}R^6; NHSO$_2$NR^{5}R^6; NHSO$_2$R^8; SO$_2$NR^{9}R^{10}; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, C_1-C_3 alkyl, (hydroxy)C_2-C_3 alkyl, $CSNR^{13}R^{14}$ or C(NH)$NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

A more preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, $CH{=}CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R^{11})-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R^{12})-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1-C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

A particularly preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-N(R^{11})-piperazinyl group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimi-

din-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of formula (I) and their pharmaceutically acceptable salts, processes for the preparation thereof, in vitro test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, pharmaceutical compositions thereof and routes of administration for human use, are described in EP-A-0463756 and EP-A-O526004.

A preliminary investigation was carried out with a view to isolating and characterising the cyclic nucleotide PDEs of human corpus cavernosum, relaxation of which leads to penile erection. Studies of substrate specificity, response to activators and inhibitor sensitivity, have demonstrated that human corpus cavernosum contains three distinct PDE enzymes.

Methods

Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2-4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250mM sucrose, 1mM EDTA, 0.5mM PMSF and 20mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with teflon pestles and soluble fraction was prepared by centrifugation at 100,000 x g for 60 min. at 4°C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1mM EDTA, 0.5 mM PMSF and 20mM HEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0-500mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500nM cGMP or 500nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1μM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10mM $CaCl_2$ and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4°C during the course of the study.

Inhibition studies were performed using a substrate concentration of 500nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3×10^{-10} to 1×10^{-4}M in half log increments. IC_{50} values were calculated using the sigmoidal curve fitting algorithm of Biostat.

Results

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represents the major PDE present and is highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE_V. Fraction II hydrolyses cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and is classified as PDE_{II}, whilst fraction III is cAMP selective and this activity is inhibited in the presence of cGMP, consistent with PDE_{III} activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE_V, whilst fraction III was clearly identified as PDE_{III}; fraction II (PDE_{II}) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE is the cGMP-specific PDE_V, whilst cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III} are also present.

The compounds of the invention have been tested in vitro and found to be potent and selective inhibitors of the cGMP-specific PDE_V. For example, one of the especially preferred compounds of the invention has an IC_{50} = 6.8 nM v.

the PDE_V enzyme, but demonstrates only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes with IC_{50} = >100 μM and 34 μM respectively. Thus relaxation of the corpus cavernosum tissue and consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

Furthermore, none of the compounds of the invention tested in rat and dog, both intravenously (i.v.) and orally (p.o.) at up to 3 mg/Kg, has shown any overt sign of adverse acute toxicity. In mouse, no deaths occurred after doses of up to 100 mg/Kg i.v.. Certain especially preferred compounds showed no toxic effects on chronic p.o. administration to rat at up to 10 mg/Kg and to dog at up to 20 mg/Kg.

In man, certain especially preferred compounds have been tested orally in both single dose and multiple dose volunteer studies. Moreover, patient studies conducted thus far have confirmed that one of the especially preferred compounds induces penile erection in impotent males.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

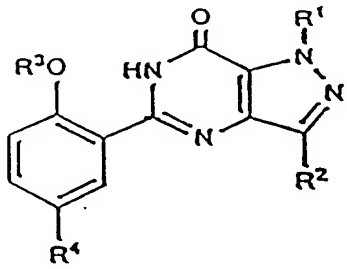
Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of formula (I) or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Moreover, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.

Claims

1. The use of a compound of formula (I):



(I)

wherein

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;
R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;
R^7 is H or C_1-C_4 alkyl;
R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;
R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, mor-

pholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}N$)C_2-C_6 alkyl; ($R^{13}R^{14}NOC$)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;

and

R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

2. The use according to claim 1 wherein in the compound of formula (I) R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl optionally substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, C_1-C_3 alkyl, (hydroxy)C_2-C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

3. The use according to claim 2 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R^{11})-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R^{12})-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1-C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

4. The use according to claim 3 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-N(R^{11})-piperazinyl group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

5. The use according to claim 4 wherein the compound of formula (I) is selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. The use according to claim 5 wherein the compound of formula (I) is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

7. The use according to claim 5 wherein the compound of formula (I) is 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

8. The use of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction.

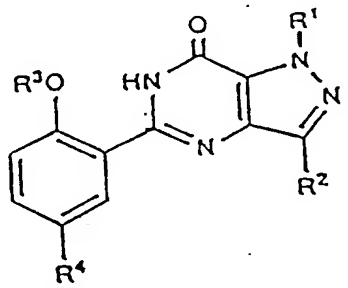
9. The use according to any one of claims 1 to 8 wherein the medicament is adapted for oral treatment.

10. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.

11. The use according to claim 10 wherein the inhibitor is a cGMP PDE_V inhibitor.

Patentansprüche

1. Verwendung einer Verbindung der Formel (I):



(I),

worin

R^1 bedeutet: H; C_1-C_3-Alkyl; C_1-C_3-Perfluoralkyl; oder C_3-C_5-Cycloalkyl;
R^2 darstellt: H; C_1-C_6-Alkyl, gegebenenfalls substituiert mit C_3-C_6-Cycloalkyl; C_1-C_3-Perfluoralkyl; oder C_3-C_6-Cycloalkyl;
R^3 ist: C_1-C_6-Alkyl, gegebenenfalls substituiert mit C_3-C_6-Cycloalkyl; C_1-C_6-Perfluoralkyl; C_3-C_5-Cycloalkyl; C_3-C_6-Alkenyl; oder C_3-C_6-Alkinyl;
R^4 bedeutet: C_1-C_4-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkenyl, gegebenenfalls substituiert mit CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkanoyl, gegebenenfalls substituiert mit NR^5R^6; (Hydroxy)-C_2-C_4-alkyl, gegebenenfalls substituiert mit NR^5R^6; (C_2-C_3-Alkoxy)-C_1-C_2-alkyl, gegebenenfalls substituiert mit OH oder NR^5R^6; $CONR^5R^6$; CO_2R^7; Halogen; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; oder Phenyl, Pyridyl, Pyrimidinyl, Imidazolyl, Oxazolyl, Thiazolyl, Thienyl oder Triazolyl, von denen jedes gegebenenfalls substituiert ist mit Methyl;
R^5 und R^6 jeweils unabhängig H oder C_1-C_4-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-N(R^{11})-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder OH;
R^7 H oder C_1-C_4-Alkyl ist;
R^8 C_1-C_3-Alkyl, gegebenenfalls substituiert mit NR^5R^6, bedeutet;
R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-N(R^{12})-Piperazinyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit C_1-C_4-Alkyl, C_1-C_3-Alkoxy, $NR^{13}R^{14}$ oder $CONR^{13}R^{14}$;
R^{11} darstellt: H; C_1-C_3-Alkyl, gegebenenfalls substituiert mit Phenyl; (Hydroxy)-C_2-C_3-alkyl; oder C_1-C_4-Alkanoyl;
R^{12} ist: H; C_1-C_6-Alkyl; (C_1-C_3-Alkoxy)-C_2-C_6-alkyl; (Hydroxy)-C_2-C_6-alkyl; ($R^{13}R^{14}$N)-C_2-C_6-Alkyl;

$(R^{13}R^{14}NOC)$-C_1-C_6-Alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; oder $C(NH)NR^{13}R^{14}$; und
R^{13} und R^{14} jeweils unabhängig H; C_1-C_4-Alkyl; (C_1-C_3-Alkoxy)-C_2-C_4-alkyl; oder (Hydroxy)-C_2-C_4-alkyl bedeuten;

oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen Behandlung von erektiler Dysfunktion bei einem männlichen Tier, einschließlich Männern.

2. Verwendung nach Anspruch 1, wobei in der Verbindung der Formel (I)

R^1 H, Methyl oder Ethyl bedeutet;
R^2 C_1-C_3-Alkyl darstellt;
R^3 C_2-C_3-Alkyl oder Allyl ist;
R^4 bedeutet: C_1-C_2-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, CN, $CONR^5R^6$ oder CO_2R^7; Acetyl, gegebenenfalls substituiert mit NR^5R^6; Hydroxyethyl, gegebenenfalls substituiert mit NR^5R^6; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; oder Pyridyl oder Imidazolyl, von denen jedes gegebenenfalls substituiert ist mit Methyl;
R^5 und R^6 jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-N(R^{11})-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder OH;
R^7 H oder tert.Butyl ist;
R^8 Methyl oder $CH_2CH_2CH_2NR^5R^6$ bedeutet;
R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino- oder 4-N(R^{12})-Piperazinyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit $NR^{13}R^{14}$ oder $CONR^{13}R^{14}$;
R^{11} H; Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt;
R^{12} H; C_1-C_3-Alkyl, (Hydroxy)-C_2-C_3-alkyl, $CSNR^{13}R^{14}$ oder $C(NH)NR^{13}R^{14}$ ist; und
R^{13} und R^{14} jeweils unabhängig H oder Methyl bedeuten.

3. Verwendung nach Anspruch 2, wobei in der Verbindung der Formel (I)

R^1 Methyl oder Ethyl bedeutet;
R^2 C_1-C_3-Alkyl darstellt;
R^3 Ethyl, n-Propyl oder Allyl ist;
R^4 $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet;
R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-N(R^{11})-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden;
R^7 H oder tert.Butyl ist;
R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-Carbamoylpiperidino- oder 4-N(R^{12})-Piperazinyl-Gruppe bilden;
R^{11} H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt; und
R^{12} H, C_1-C_3-Alkyl, 2-Hydroxyethyl oder $CSNH_2$ ist.

4. Verwendung nach Anspruch 3, wobei in der Verbindung der Formel (I)

R^1 Methyl oder Ethyl bedeutet;
R^2 n-Propyl darstellt;
R^3 Ethyl, n-Propyl oder Allyl ist;
R^4 $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ oder 1-Methyl-2-imidazolyl bedeutet;
R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Morpholino- oder 4-N(R^{11})-Piperazinyl-Gruppe bilden;
R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-N(R^{12})-Piperazinyl-Gruppe bilden;
R^{11} Methyl oder Acetyl darstellt; und
R^{12} H, Methyl, 2-Propyl oder 2-Hydroxyethyl ist.

5. Verwendung nach Anspruch 4, wobei die Verbindung der Formel (I) ausgewählt wird aus:

5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[2-Allyloxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-{2-Ethoxy-5-[4-(2-propyl)-1-piperazinylsulfonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-{2-Ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulfonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-{5-[4-(2-Hydroxyethyl)-1-piperazinylsulfonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on; und
5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on.

6. Verwendung nach Anspruch 5, wobei die Verbindung der Formel (I) 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on ist.

7. Verwendung nach Anspruch 5, wobei die Verbindung der Formel (I) 5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on ist.

8. Verwendung einer Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 7 definiert, oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen Behandlung weiblicher sexueller Dysfunktion.

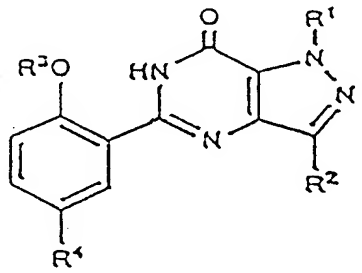
9. Verwendung nach einem der Ansprüche 1 bis 8, wobei das Medikament für eine orale Behandlung geeignet ist.

10. Verwendung eines cGMP PDE-Inhibitors, oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen oralen Behandlung von erektiler Dysfunktion bei Männern.

11. Verwendung nach Anspruch 10, wobei der Inhibitor ein cGMP PDE_V-Inhibitor ist.

Revendications

1. Utilisation d'un composé de formule (I) :



(I)

dans laquelle :

R^1 représente H ; alkyle en C_1-C_3 ; perfluoroalkyle en C_1-C_3 ; ou cycloalkyle en C_3-C_5 ;
R^2 représente H ; alkyle en C_1-C_6 facultativement substitué par cycloalkyle en C_3-C_6 ; perfluoroalkyle en C_1-C_3 ; ou cycloalkyle en C_3-C_6 ;

R^3 représente alkyle en C_1-C_6 facultativement substitué par cycloalkyle en C_3-C_6 ; perfluoroalkyle en C_1-C_6 ; cycloalkyle en C_3-C_5 ; alkényle en C_3-C_6 ; ou alkynyle en C_3-C_6 ;
R^4 représente alkyle en C_1-C_4 facultativement substitué par OH, NR^5R^6, CN, $CONR^5R^6$ ou CO_2R^7 ; alkényle en C_2-C_4 facultativement substitué par CN, $CONR^5R^6$ ou CO_2R^7 ; alcanoyle en C_2-C_4 facultativement substitué par NR^5R^6 ; (hydroxy)alkyle en C_2-C_4 facultativement substitué par NR^5R^6 ; (alcoxy en C_2-C_3)alkyle en C_1-C_2 facultativement substitué par OH ou NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halogéno ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; ou phényle, pyridyle, pyrimidinyle, imidazolyle, oxazolyle, thiazolyle, thiényle ou triazolyle dont l'un quelconque est facultativement substitué par méthyle ;
R^5 et R^6 représentent chacun indépendamment H ou alkyle en C_1-C_4, ou représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pyrrolidinyle, pipéridino, morpholino, 4-N(R^{11})-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou OH ;
R^7 représente H ou alkyle en C_1-C_4 ;
R^8 représente alkyle en C_1-C_3 facultativement substitué par NR^5R^6 ;
R^9 et R^{10} représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pyrrolidinyle, pipéridino, morpholino ou 4-N(R^{12})-pipérazinyle, ledit groupe étant facultativement substitué par alkyle en C_1-C_4, alcoxy en C_1-C_3, $NR^{13}R^{14}$ ou $CONR^{13}R^{14}$;
R^{11} représente H ; alkyle en C_1-C_3 facultativement substitué par phényle ; (hydroxy)alkyle en C_2-C_3 ; ou alcanoyle en C_1-C_4 ;
R^{12} représente H ; alkyle en C_1-C_6 ; (alcoxy en C_1-C_3)alkyle en C_2-C_6 ; (hydroxy)alkyle en C_2-C_6 ; ($R^{13}R^{14}$N)alkyle en C_2-C_6 ; ($R^{13}R^{14}$NOC)alkyle en C_1-C_6 ; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; ou $C(NH)NR^{13}R^{14}$; et
R^{13} et R^{14} représentent chacun indépendamment H, alkyle en C_1-C_4 ; (alcoxy en C_1-C_3)alkyle en C_2-C_4 ; ou (hydroxy)alkyle en C_2-C_4 ;

ou un sel pharmaceutiquement acceptable, ou une composition pharmaceutique contenant ledit composé ou ledit sel, pour la fabrication d'un médicament en vue du traitement curatif ou prophylactique d'un dysfonctionnement érectile chez un animal mâle, y compris l'homme.

2. Utilisation selon la revendication 1, dans laquelle, dans le composé de formule (I), R^1 représente H, méthyle ou éthyle ; R^2 représente alkyle en C_1-C_3 ; R^3 représente alkyle en C_2-C_3 ou allyle ; R^4 représente alkyle en C_1-C_2 facultativement substitué par OH, NR^5R^6, CN, $CONR^5R^6$ ou CO_2R^7 ; acétyle facultativement substitué par NR^5R^6 ; hydroxyéthyle facultativement substitué par NR^5R^6 ; éthoxyméthyle facultativement substitué par OH ou NR^5R^6 ; CH=CHCN ; CH=CHCONR^{5}R^6 ; CH=CHCO$_2$R^7 ; CONR^{5}R^6 : CO$_2$H ; Br ; NR^{5}R^6 ; NHSO$_2$NR^{5}R^6 ; NHSO$_2$R^8 ; SO$_2$NR^{9}R^{10} ; ou pyridyle ou imidazolyle dont l'un quelconque est facultativement substitué par méthyle ; R^5 et R^6 représentent chacun indépendamment H, méthyle ou éthyle, ou représentent ensemble, avec l'atome d'azote auquel ils sont liés un groupe pipéridino, morpholino, 4-N(R^{11})-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou OH ; R^7 représente H ou t-butyle ; R^8 représente méthyle ou $CH_2CH_2CH_2NR^5R^6$; R^9 et R^{10} représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pipéridino ou 4-N(R^{12})-pipérazinyle, ledit groupe étant facultativement substitué par $NR^{13}R^{14}$ ou $CONR^{13}R^{14}$; R^{11} représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle ; R^{12} représente H, alkyle en C_1-C_3, (hydroxy)alkyle en C_2-C_3, $CSNR^{13}R^{14}$ ou $C(NH)NR^{13}R^{14}$; et R^{13} et R^{14} représentent chacun indépendamment H ou méthyle.

3. Utilisation selon la revendication 2, dans laquelle, dans le composé de formule (I), R^1 représente méthyle ou éthyle ; R^2 représente alkyle en C_1-C_3 ; R^3 représente éthyle, n-propyle ou allyle ; R^4 représente $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, CH=CHCO$_2$R^7, CONR^{5}R^6, CO$_2$H, Br, NHSO$_2$NR^{5}R^6, NHSO$_2$CH$_2$CH$_2$CH$_2$NR^{5}R^6, SO$_2$NR^{9}R^{10}, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R^5 et R^6 représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4-N(R^{11})-pipérazinyle ou 2-méthyl-1-imidazolyle ; R^7 représente H ou t-butyle ; R^9 et R^{10} représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe 4-carbamoylpipéridino ou 4-N-(R^{12})-pipérazinyle ; R^{11} représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle et R^{12} représente H, alkyle en C_1-C_3, 2-hydroxyéthyle ou $CSNH_2$.

4. Utilisation selon la revendication 3, dans laquelle, dans le composé de formule (I), R^1 représente méthyle ou éthyle ; R^2 représente n-propyle ; R^3 représente éthyle, n-propyle ou allyle ; R^4 représente $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ ou 1-méthyl-2-imidazolyle ; R^5 et R^6 représentent ensemble, avec l'atome d'azote auquel ils sont liés un groupe morpholino ou 4-N(R^{11})-pipérazinyle ; R^9 et R^{10} représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe 4-N(R^{12})-pipérazinyle ; R^{11} représente méthyle ou acétyle ; et R^{12} représente H, méthyle, 2-propyle ou 2-hydroxyéthyle.

5. Utilisation selon la revendication 4, dans laquelle le composé de formule (I) est choisi parmi :

la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylsulphonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-allyloxy-5-(4-méthyl-1-pipérazinylsulphonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-{2-éthoxy-5-[4-(2-propyl)-1-pipérazinylsulphonyl]phényl}-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-{2-éthoxy-5-[4-(2-hydroxyéthyl-1-pipérazinylsulphonyl]phényl}-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-{5-[4-(2-hydroxyéthyl)-1-pipérazinylsulphonyl]-2-n-propoxyphényl}-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ; et
la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. Utilisation selon la revendication 5, dans laquelle le composé de formule (I) est la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylsulfonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

7. Utilisation selon la revendication 5, dans laquelle le composé de formule (I) est la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3d]pyrimidin-7-one.

8. Utilisation d'un composé de formule (I) tel que défini dans l'une quelconque des revendications 1 à 7, ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou d'une composition pharmaceutique contenant ledit composé ou ledit sel pour la fabrication d'un médicament pour le traitement curatif ou prophylactique d'un dysfonctionnement sexuel féminin.

9. Utilisation selon l'une quelconque des revendications 1 à 8, dans laquelle le médicament est adapté à un traitement par voie orale.

10. Utilisation d'un inhibiteur de la cGMP PDE, ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou d'une composition pharmaceutique contenant ledit composé ou ledit sel, pour la fabrication d'un médicament pour le traitement curatif ou prophylactique par voie orale d'un dysfonctionnement érectile chez l'homme.

11. Utilisation selon la revendication 10, dans laquelle l'inhibiteur est un inhibiteur de la cGMP PDE_V.